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Mazdoor Kisan Shakti Sangathan

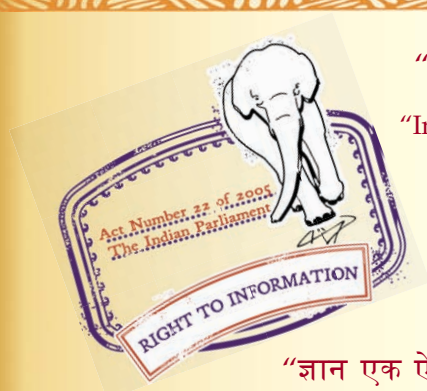
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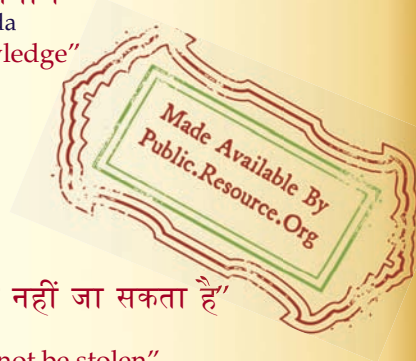
IS 12572-6 (1988): Guide for evaluation of medical devices for biological hazards, Part 6: Method of test for systemic toxicity; assessment of pyrogenicity in rabbits of extracts from medical devices [MHD 12: Hospital Equipment]



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“ज्ञान एक ऐसा खजाना है जो कभी चुराया नहीं जा सकता है”

Bhartrhari—Nitiśatakam

“Knowledge is such a treasure which cannot be stolen”

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Indian Standard

(Reaffirmed 2006)

GUIDE FOR EVALUATION OF MEDICAL DEVICES FOR BIOLOGICAL HAZARDS

PART 6 METHOD OF TEST FOR SYSTEMIC TOXICITY : ASSESSMENT
OF PYROGENICITY IN RABBITS OF EXTRACTS FROM
MEDICAL DEVICES

भारतीय मानक

जैव-वैज्ञानिक खतरों के लिए चिकित्सीय युक्तियों के मूल्यांकन की मार्गदर्शिका

भाग 6 चिकित्सीय युक्तियों के निष्कर्षों की खरगोशों में अरिमजनिकता की
विषालुता के क्रमबद्ध मूल्यांकन की परीक्षण पद्धति

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DESCRIPTORS : MEDICAL DEVICES. BIOLOGICAL HAZARDS. SYSTEMIC
TOXICITY. PYROGENICITY.

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FOREWORD

This Indian Standard (Part 6) was adopted by the Bureau of **Indian** Standards on 14 September 1988, after the draft finalized by the Medical Glass Instruments and Appliances Sectional Committee had been approved by the Consumer Products and Medical Instruments Division Council.

This part (Part 6) of the standard is one of a series of methods of test for assessing the biological hazards of medical devices that directly contact body tissues or substances that are to be introduced into the body by means other than oral.

The test in this standard has been selected to indicate the presence of pyrogenic substances in or on a device, although it is recognized that pyrogens of microbial origin will be detected, if present.

In some cases, the pyrogenicity caused by gram negative endotoxaemia can be detected by the LAL test which can be employed as an additional test. This, however, does not exclude some of the requirements of the pyrogen test, particularly when LAL test is negative.

This standard is proposed to be published in 12 parts. Other parts are as follows:

- Part 1 Terminology
- Part 2 Selection of biological methods of test
- Part 3 Method of testing by tissue implantation
- Part 4 Method of test for systemic toxicity: Assessment of acute toxicity of extracts from medical devices
- Part 5 Method of test for intracutaneous reactivity of extracts from medical devices
- Part 7 Methods of test for sensitization: Assessment of potential of medical devices to produce delayed contact dermatitis
- Part 8 Methods of test for skin irritation of extracts from medical devices
- Part 9 Method of test for skin irritation of solid medical devices
- Part 10 Method of test for dental materials
- Part 11 **Metho**d of test for eye irritation
- Part 12 Method of test for toxicity to cells in culture of extracts from medical devices

Part 2 of this standard provides guidance on the **selection** of recommended methods of test for initial assessment of biological hazards in medical devices which has ~~been~~ referred to in this standard.

In the preparation of this standard, assistance has been derived from BS 5736 :**Part 5** : 1982 'Evaluation of medical devices for biological hazards: Part 5 Method of test for systemic toxicity; **Assessment** of pyrogenicity in rabbits of ~~extracts from~~ medical devices', issued by the British Standards Institution, UK.

Indian Standard

GUIDE FOR EVALUATION OF MEDICAL DEVICES FOR BIOLOGICAL HAZARDS

PART 6 METHOD OF TEST FOR SYSTEMIC TOXICITY : ASSESSMENT OF PYROGENICITY IN RABBITS OF EXTRACTS FROM MEDICAL DEVICES

I SCOPE

1.1 This standard (Part 6) describes a method of test designed to identify the presence of pyrogenic materials in or on medical devices. This method specifies measurement of the rise in body temperature of rabbits during a period of 3 h following an intravenous injection of an extract of the device, prepared with pyrogen-free saline.

1.2 This method of test is recommended for the initial assessment of devices in Categories A, **B₁**, C and **E₁** (see Part 2 of this standard):

- a) *Category A* — Those devices intended for long-term (long-term covers a period from a few months to permanent use) implantation within the body tissue, for example, artery grafts and hip prostheses;
- b) *Category B₁* — Those devices intended for **long-term** (long-term covers a period from a few months to permanent use) or repeated contact with mucosal surfaces, for example, contraceptive devices;
- c) *Category C* — Those devices intended for short-term (short-term covers a period from a few minutes to several weeks continuous use) use within the body or in contact with the mucosal surfaces, for example, tracheal tubes, urinary catheters and intravenous cannulae;
- d) *Category E₁* — Those devices intended to contain or administer substances, including blood, that are introduced *parantrally* into the body, for example, blood bags, hemodialysis equipment, intravenous administration sets and kits and hypodermic syringes.

2 DEFINITIONS

For the purpose of this standard, the following definitions shall apply.

2.1 Final Product

Medical device in its ready-for-use state.

2.2 Initial Temperature

The mean of two temperatures taken at a **30 minutes** interval in the 40 minutes preceding injecting of the extract.

2.3 Maximum Temperature

The highest temperature recorded in 3 hours following the injection of the extract.

2.4 Medical Device

Any item used in medical treatment, diagnosis or contraception, not intended to have a **pharmacological** action on the body.

2.5 Pyrogen

A fever producing substance.

2.6 Response

The difference between the maximum temperature and the initial temperature of each rabbit.

2.7 Summed Response

The sum of responses of the rabbits selected for the main test.

2.8 Test Material

The final product or sample of final product that is to be tested.

3 ANIMALS AND HUSBANDRY

3.1 A minimum of three healthy adult rabbits of either sex, weighing not less than 1.5 kg each, shall be used (*see 5.3.1*).

3.2 The animals shall be housed individually in an area of uniform temperature, controlled to within $\pm 3^{\circ}\text{C}$, and kept free from disturbances likely to excite them.

3.3 The animals shall have free access to food and water, except as specified in 5.3.2 and 5.3.3. The diet shall not contain antibiotics.

4 PREPARATION OF EXTRACTS

4.1 Sterilization and Handling of Test Material

4.1.1 Pyrogen-free glassware, syringes and needles shall be used throughout the test procedure.

4.1.2 Test material that is, pre-sterilized (refers to devices obtained from the manufacturer or supplier sterilized) shall be handled aseptically throughout the extraction and test procedure.

4.1.3 Test material that is normally supplied non-sterile but is sterilized before use shall be sterilized before the extraction procedure and handled aseptically throughout the extraction and test procedure.

4.1.4 Test material not required to be sterile in use shall either be prepared as specified in 4.1.3 or if such devices cannot be sterilized, the extraction procedure shall be carried out at not less than 60°C to minimize bacterial growth, and the extracts obtained shall be sterilized before administration.

4.2 Extractant

Pyrogen-free sterile saline solution containing 9 g/l sodium chloride shall be used.

4.3 Principles of Extraction

4.3.1 The test material shall be representative of the final product.

4.3.1.1 To achieve this, the test material may consist of one or more intact devices or, if more appropriate, may consist of small pieces of the final product. For large multicomponent devices (for example, dialysis units or membrane oxygenators), it may be appropriate to separately test the individual components of the device.

4.3.2 If possible, the volume of extractant selected should be such that it permits injection into a single rabbit of not less than 90 percent of the extract obtained from a single device.

4.3.3 The technique used in exposing the test material to the extractant shall be selected according to the requirements of 4.3.1 and 4.3.2, and may consist of total immersion or flow-through methods, or a successive extraction of more than one specimen of the final product.

4.3.4 Extraction conditions, within the requirements of 4.1.4, shall simulate as nearly as possible the conditions under which the device will normally be used.

4.3.5 During the extraction, 27 ± 3 °C shall be representative of room temperature and 37 ± 2 °C that of the body temperature.

4.4 Procedure

4.4.1 Prepare a sufficient volume of extract to carry out the test procedure on three rabbits (see 7.5).

4.4.2 Ensure a time of contact between extractant and sample which, within the requirements of 4.1.4, simulates the conditions under which the device will normally be used, except that it shall be not less than 2 h and need not be longer than 72 h.

4.4.3 Sterilize any extract obtained from unsterilized devices (see 4.1.4).

4.4.4 Record for the test report, the precise conditions of extraction.

5 TEST PROCEDURE

5.1 Apparatus

5.1.1 Rabbit Retaining Boxes

These shall be of open design with loose-fitting neck stocks so as to permit the animals to sit in a normal resting position.

5.1.2 Thermocouple or Thermistor Probe Thermometers

These shall have an accuracy of ± 0.1 °C.

5.2 Suitability of Animals

A rabbit shall not be used in the pyrogenicity test if:

- a) it has been used in the preceding three days for a pyrogenicity test; or
- b) it has been used, in the preceding three weeks, for a pyrogenicity test in which the extract under examination produced a summed response exceeding 1 °C; or
- c) it has been used, at any time, for a pyrogenicity test in which the mean response of the rabbits in the batch exceeded 1.2 °C; or
- d) any typical body weight loss has occurred during the week preceding the test.

5.3 Preparation of Animals

5.3.1 For complete assessment of preliminary and main tests (see 5.4 and 5.5), results are required for three suitable rabbits (It may be necessary to have more than three rabbits available because of possible exclusion, by the criteria laid down in 5.4.6 and 5.5.3, of animals unsuitable for the tests).

5.3.2 Withhold food from the rabbits the night before any test and until the completion of the test.

5.3.3 Withhold water from the rabbits during the test.

5.3.4 Maintain the rabbits throughout the test procedure, in environmental conditions similar to those in which the animals are housed.

5.3.5 Weigh the rabbits and record the results.

5.3.6 Not less than one hour before any temperature measurement, transfer each rabbit to a retaining box and insert a thermometer into the rectal tract to a depth of between 50 and 75 mm. Use appropriate means to maintain the thermometer in a fixed position throughout the tests.

5.4 Preliminary Test

5.4.1 Conduct the preliminary test, one to three days before the main test.

5.4.2 Warm the pyrogen-free sterile saline solution to $38.5 \pm 1.0^\circ\text{C}$.

5.4.3 Record the temperature of each rabbit at 30 minutes intervals, beginning 90 minutes before injection.

5.4.4 Slowly inject via the marginal (lateral) vein of one ear of each rabbit, 10 ml/kg of pyrogen-free sterile saline solution. The duration of injection shall not exceed 4 minutes.

5.4.5 Continue to record the temperature of each rabbit at 30 minutes intervals for 3 hours after injection.

5.4.6 Reject from use in the main test all animals which show a difference in excess of 0.6°C between the highest and the lowest recorded temperatures.

5.5 Main Test

5.5.1 Record the pre-injection temperatures of each rabbit at 30 minutes intervals, beginning **not less than** 90 minutes before injection and determine the initial temperature (*see* 2.2).

5.5.2 Identify those rabbits which are to receive the test extract according to the following criteria:

- a) A rabbit shall be excluded from the test, if the difference between any two consecutive readings exceeds 0.2°C .
- b) A rabbit shall be excluded from the test, if the range of temperature readings exceeds 0.4°C .

c) A rabbit shall be excluded from the test, if the initial temperature is not between 38.0°C and 39.8°C .

5.5.3 Select three rabbits whose initial temperatures before Injection do not differ by more than 1.0°C .

5.5.4 Warm the extract to $38.5 \pm 1.0^\circ\text{C}$.

5.5.5 Inject, as described in 5.4.4, the extract into each of the three rabbits.

5.5.6 Record the temperature of each rabbit at 30 minutes intervals for 3 hours after injection and note the maximum temperature (*see* 2.3).

6 PRESENTATION OF RESULTS

The results shall be submitted in a test report that includes a complete record of the method of extraction and procedures followed and any other relevant data used in the assessment of results as described in 7.

7 ASSESSMENT OF RESULTS

7.1 The assessment of the results should be carried out by an experienced person (preferably a toxicologist) who is aware of the conditions of use of the final product and has with him the appropriate chemical and biological data concerning it (*see* 3.3 and 3.4 of Part 2 of this standard).

7.2 The overall assessment of the pyrogenicity of medical device shall be carried out by taking into consideration all the information given in the test report.

7.3 Negative values for the response shall be taken as zero.

7.4 Assessment shall be based on the summed responses of the selected rabbits.

7.5 Extract producing summed responses in excess of 2.65°C shall be considered to be pyrogenic.

7.6 If the summed responses fall between 1.15 and 2.65°C , the test shall be repeated on three additional rabbits. Extract shall be considered to be pyrogenic if the summed responses in all six rabbits exceeds 2.8°C .

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